FIRST RESPONSE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Eva Sevick-Muraca, et al.
Serial No.:	09/870,144
Filing Date:	May 30, 2001
Confirmation No.	9131
Art Unit No.	3737
Examiner:	Lin Yeoyuh
Title:	**IMAGING OF LIGHT SCATTERING TISSUES**
	WITH FLUORESCENT CONTRAST AGENTS

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>
> _Willie Jiles_
> Willie Jiles
>
> Date: January 12, 2004

Dear Sir:

RESPONSE PURSUANT TO 37 C.F.R. 1.111

In response to the Office Action mailed September 12, 2003, Applicants respectfully request the Examiner to reconsider the rejection of the claims in view of the following amendments thereto, and the comments as set forth below. Please amend the application as follows:

In the Abstract

Please amend the abstract as follows:

A system and method for non-invasive biomedical optical imaging and spectroscopy with low-level light is described. The technique ~~consists~~ includes ~~of~~ a modulated light source coupled to tissue to introduce excitation light. Fluorescent light emitted in response to the excitation light is detected with a sensor. The AC intensity and phase of the excitation and detected fluorescent light is provided to a processor operatively coupled to the sensor. A processor employs the measured emission kinetics of excitation and fluorescent light to "map" the spatial variation of one or more fluorescence characteristics of the tissue and generate a corresponding image of the tissue via an output device. The fluorescence characteristic may be provided by exogenous contrast agents, endogenous fluorophores, or both. A technique to select or design an exogenous fluorescent contrast agent to improve image contrast is also disclosed.

In the Specification

Please amend the first paragraph appearing on page 1, line 3, by adding a title in front of the paragraph, and adding text to the paragraph as follows:

CROSS-REFERENCE TO RELATED APPLICATION:

This application is a continuation of U.S. Application No. 09/367,148, filed November 22, 1999, which was the National Stage of International Application No. PCT/US/98/02354, filed February 6, 1998, which claims the benefit of U.S. Provisional Application No. 60/039,318, filed February 7, 1997 and which is a continuation-in-part of U.S. Patent No. 5,865,754.

Amendments to the Claims

Please amend the claims as follows.

1.   (Original) A method, comprising:

introducing an exogenous fluorescent contrast agent into a biologic tissue, the tissue multiply scattering light with a mean time-of-flight, and the agent having a fluorescence lifetime within a factor of about ten of the mean time-of- flight;

exposing the tissue to an excitation light with a predetermined time-varying intensity;

detecting a light emission from the tissue in response to said exposing;

generating an image of the tissue by mapping spatial variation of a level of a fluorescence characteristic of the tissue from the light emission in accordance with a mathematical expression modeling multiple light scattering behavior of the tissue; and

wherein the agent is selected in accordance with a predetermined relationship between degree of image contrast and at least one of fluorescence yield or the fluorescence lifetime.

2.   (Original) The method of claim 1, wherein the at least one is fluorescence lifetime.

3.   (Original) The method of claim 1, wherein the fluorescence lifetime is in a range of about 0.1 to 10 nanoseconds.

4.   (Original) The method of claim 1, wherein the fluorescence lifetime is in a range of about 0.5 to 5 nanoseconds.

5.   (Original) The method of claim 1, wherein the fluorescence lifetime is in a range of about 0.2 to 2 nanoseconds.

6.   (Original) The method of claim 1, wherein the mathematical expression corresponds to a diffusion equation approximation of multiply scattered light.

7.   (Original) The method of claim 1, wherein the fluorescence characteristic is at least one of fluorescence lifetime, fluorescence yield, or fluorescence quantum efficiency.

8.   (Original)   The method of claim **1,** wherein said generating includes determining a modulation amplitude change and a phase change of the light emission relative to the excitation light.

9.   (Original)   The method of claim 8, wherein the fluorescence characteristic corresponds to the fluorescence lifetime.

10.   (Original) The method of claim 9, wherein the mathematical expression is in a frequency domain form and the image contrast is provided in terms of at least one of phase shift contrast or modulation contrast.

11.   (Original) A method comprising:

selecting a fluorescent contrast agent as a function of a predetermined time-of-flight for a tissue to be imaged in accordance with a mathematical expression modeling the behavior of multiply scattered light traveling through the tissue, the fluorescent contrast agent have a fluorescence lifetime within a factor of ten of the predetermined time-of-flight; and

providing the fluorescent agent for introduction into the tissue.

12.   (Original) The method of claim 11, wherein the fluorescence lifetime is in a range of about 0.1 to 10 nanoseconds.

13.   (Original) The method of claim 11, wherein the fluorescence lifetime is in a range of about 0.5 to 5 nanoseconds.

14.   (Original) The method of claim 11, wherein the fluorescence lifetime is in a range of about 0.2 to 2 nanoseconds.

15.   (Original) The method of claim 11, wherein the mathematical expression corresponds to a diffusion equation approximation of multiply scattered light.

16.   (Original) The method of claim 11, further comprising generating an image of the tissue by mapping spatial variation of a level of a fluorescence characteristic of the tissue.

17.   (Original) A method, comprising:

evaluating ability of a number of fluorescent agents to provide image contrast between different tissue types, said evaluating including determining a relationship between degree of image contrast and at least one of fluorescence lifetime or fluorescence yield of the agent;

selecting one of the agents based on said evaluating; and

providing the selected one of the agents for introduction into a biologic tissue to enhance imaging performed in accordance with a mathematical expression modeling the behavior of multiply scattered light traveling through the tissue.

18.   (Original) The method of claim 17, wherein the at least one is fluorescence lifetime.

19.   (Original) The method of claim 17, wherein the mathematical expression corresponds to a diffusion equation approximation of multiply scattered light.

20.   (Original) The method of claim 19, further comprising applying the diffusion equation approximation in a frequency domain form.

21.   (Original) The method of claim 17, further comprising generating an image of the tissue by mapping spatial variation of a level of a fluorescence characteristic of the tissue.

22.   (Original) The method of claim 17, wherein the mathematical expression is in a frequency domain form and the image contrast is provided in terms of at least one of phase shift contrast or modulation contrast.

23.   (Original) A method, comprising:

exposing a biologic tissue to a first excitation light;

detecting a first emission from the tissue in response to the first excitation light;

introducing a fluorescent contrast agent into the tissue after said detecting;

exposing the tissue after said introducing to a second excitation light;

sensing a second emission in response to the second excitation light;

comparing data corresponding to the first emission with data corresponding to the second emission to evaluate contrast provided by the agent as a function of at least one of fluorescence lifetime, fluorescence yield, or quantum efficiency.

24.   (Original) The method of claim 23, wherein the at least one is fluorescence lifetime.

25.   (Original) The method of claim 24, wherein the fluorescence lifetime is in a range of about 0.1 to 10 nanoseconds.

26.   (Original) The method of claim 24, wherein the fluorescence lifetime is in a range of about 0.5 to 5 nanoseconds.

27.   (Original) The method of claim 24, wherein the fluorescence lifetime is in a range of about 0.2 to 2 nanoseconds.

28.   (Original) The method of claim 23, further comprising evaluating the first and second emissions with a mathematical expression modeling the behavior of multiply scattered light traveling through the tissue.

29.   (Original) The method of claim 28, wherein the mathematical expression corresponds to a diffusion equation approximation of multiply scattered light.

30.   (Original) The method of claim 23, further comprising generating an image of the tissue by mapping spatial variation of a level of a fluorescence characteristic of the tissue.

31.   (Original) The method of claim 30, wherein the fluorescence characteristic is at least one of fluorescence lifetime, fluorescence yield, or fluorescence quantum efficiency.

32.   (Original) The method of claim 30, wherein said generating includes determining a modulation amplitude change and a phase change of the light emission relative to the excitation light.

33.   (Original) The method of claim 32, wherein the fluorescence characteristic corresponds to the fluorescence lifetime.

34.   (Original) The method of claim 23, wherein wavelength of the first excitation light is generally the same as wavelength of fluorescent light emitted by the agent in response to the second excitation light.

REMARKS

This application has been carefully reviewed in light of the Office Action mailed September 12, 2003. Claims 1-34 are pending and stand rejected. No amendments have been made. Reconsideration and allowance of Claims 1-34 is respectfully requested in view of the following remarks.

Examiner Interview

Applicants express appreciation to the Examiner for the telephone interview conducted on November 17, 2003. In that interview, the objection to the oath declaration was discussed. In particular, it was discussed that certain claims to priority were made both as domestic claims and as foreign clams and that correction is required. Applicants appreciate the Examiner's indication in that interview that a revised oath/declaration may be submitted at a date subsequent to this Response to allow time to obtain appropriate signatures from the inventors.

In The Specification

The abstract has been amended as suggested by the Examiner. Favorable action is requested. Paragraph 1 of the Office Action addresses amending the specification to make any desired claim to priority. Applicants note that the first page of the specification, which includes the title, also includes a related applications section. The related applications sections of the specification has been amended to be consistent with the declaration. This amendment does not require a petition under 37 CFR 1.78(a)(3) at least because the claim to priority was presented in the application at the time of filing in the declaration.

In the Oath/Declaration

As described above, a new declaration will be submitted in compliance with 37 CFR 1.67(a) after receipt from the inventors. Favorable action is requested.

Rejections Under 35 U.S.C. § 103(a)

The Office Action rejects Claims 1-5, 7-14, 16-18, 21-28, and 30-34 under 35 U.S.C. § 103(a) as being unpatentable over Lakowicz et al. (Pat. No. 5,485,530), and the Office Action rejects Claims 6, 15, 19, 20, and 29 under 35 U.S.C. § 103(a) as being unpatentable

over Lakowicz et al., as applied to claims 1, 27, 33, and 39 above, and further in view of Sevick-Muraca et al. (Pat. No. 5,865,754). In addition, claims 1-34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sevick-Muraca, and further in view of Lacowicz. Applicants respectfully traverse these rejections for the reasons discussed below.

Claim 11 is allowable at least because the references cited above do not teach or suggest "selecting a fluorescent contrast agent as a function of a predetermined time-of-flight for a tissue to be imaged in accordance with a mathematical expression modeling the behavior of multiply scattered light traveling through the tissue, the fluorescent contrast agent have a fluorescence lifetime within a factor of ten of the predetermined time-of-flight." The Office Action asserts that this limitation is not shown in either reference, but nevertheless rejects this claim arguing that "it would have been an obvious matter of design choice to one of ordinary skill in the art at the time the invention was made to select a contrast agent fitting of the said limitation in order to maximize contrast and image clarity," Office Action, page 5. But this is incorrect.

It is the teachings of the invention that state the desirable relationship between the mean time-of flight of the multiply scattered light and the fluorescence lifetime of the contrast agent. This facilitates detection of the multiply scattering light and therefore imaging within tissue. The science and mathematics behind this relationship between the mean time-of-flight and the fluorescence lifetime is complicated and described through example in detail in the Applicant's specification at Example 4, Figures 16 through 20; however, an analogy is provided here for the convenience of the Examiner. It is emphasized that this description is provided to facilitate the Examiner's understanding of why it would not be obvious to modify the references as proposed by the Examiner and is not intended to be a completely accurate description of the operation of the invention, and does not limit the invention of Claim 11.

The detection of the multiple scattering light may be thought of as analogous to detecting light from a series of progressively dimmer light bulbs lined up along the line of sight of a detector such that the detector can only see the first light bulb in the line. This is analogous to detecting fluorescence at the tissue surface that is generated from deeper and deeper tissue regions. Because excitation light exponentially attenuates as it propagates deep into the tissue, the strength of the fluorescent "source" or light bulb also becomes exponentially weaker with increased distance inside the tissue from the surface of the

illuminated tissue. As excitation light propagates and attenuates during its travel deep into the tissue, it therefore turns on the closest light bulb at the surface, say a 10Watt bulb, and successively lower wattage bulbs, 0.1 Watt, 1 microWatt, etc. as the excitation light propagates in time away from the tissue surface.

Consider the case of short-lifetimes, such that the photon migration times (or the time it reaches for excitation light to travel deep into the tissue) are longer than the fluorphore lifetime or the time of which the light bulbs are turned off. When the first light bulb is turned off (as could be the case with a short-lived fluorophore), then the second, dimmer-bulb may be seen. In this analogy, the light bulbs correspond roughly to the fluorescent contrast agent. Thus, to detect multiply scattered fluorescent light deep within a tissue, the "light bulbs" in the front of the line need to fluoresce, but then need to turn off quickly enough such that the "light bulbs" in the back of the line may also be seen before they turn off. Conversely, if the fluorescent lifetime is long in comparison to the photon "time-of-flight" than the 10W bulb will "swamp" out the small amount of light from the deeper and dimmer bulbs and consequently, not enabling them to be seen. This example corresponds roughly to a desirable relationship between the fluorescent lifetime of the agent and the mean time of flight of the scattering light.

Indeed, Figures 17A and B of the present application show that the change in measurement variable (phase and modulation ratio) change as a function of fluorescent target position when the fluorescent lifetimes are smaller than or within the same order of magnitude of photon "time-of-flight" but that such changes disappear when the lifetime is much larger than the photon "time-of-flight." Figures 17-20 directly show mathematical predictions and experimental measurements. The present invention recognizes — and the present specification describes — the derivation of desirable relationships between this time of flight and the fluorescent lifetime. It is respectfully submitted that the cited references provide no evidence that the claimed relationship would be obvious to one of skill in the art. Indeed, the assertion in the Office Action that "it would have been an obvious matter of design choice to one of ordinary skill in the art at the time the invention was made to select a contrast agent fitting of the said limitation in order to maximize contrast and image clarity" is conclusory and is supported by no objective evidence, which is not permissible.

Applicants respectfully submit that the rejection of Claim 11 is improper because the references do not teach this missing limitation and there is no suggestion or motivation in the

references or in the knowledge generally available to one of ordinary skill in the art at the time of the invention to combine the cited references as proposed. Nothing in *Sevick-Muraca*, or *Lackowicz* suggests or motivates the proposed combination of references, nor has the Office Action provided evidence that suggests the proposed combination.[1] Speculation in hindsight that "it would have been obvious" to make the proposed combination or modification because doing so would be helpful is insufficient under the M.P.E.P.[2] and governing Federal Circuit case law."[3]

For at least this reason that the cited references to not teach or suggest "selecting a fluorescent contrast agent as a function of a predetermined time-of-flight for a tissue to be imaged in accordance with a mathematical expression modeling the behavior of multiply scattered light traveling through the tissue, the fluorescent contrast agent have a fluorescence lifetime within a factor of ten of the predetermined time-of-flight" the claim is allowable, as are the claims depending therefrom. Favorable action is requested. Independent claims 1, 17, and 23 are believed allowable for analogous reasons, as are the claims depending therefrom. Favorable action is requested.

In addition to being allowable for the reasons described above, all claims are also allowable over *Lakowicz* because *Lakowicz* does not teach the use of multiply scattering light. As described in the specification, in one embodiment multiple scattering light is used

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[1] If "common knowledge" or "well known" art is being relied on to combine the references, Applicants respectfully request that a reference be provided in support of this position pursuant to M.P.E.P. § 2144.03. If personal knowledge is being relied on to supply the required motivation or suggestion to combine, Applicants respectfully request that an affidavit supporting such facts be provided pursuant to M.P.E.P. § 2144.03.

[2] *See* M.P.E.P. § 2145 X.C. ("The Federal Circuit has produced a number of decisions overturning obviousness rejections due to a lack of suggestion in the prior art of the desirability of combining references.)

[3] For example, in *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999), the Federal Circuit reversed a finding of obviousness by the Board of Patent Appeals and Interferences, explaining that evidence of a suggestion, teaching, or motivation to combine is essential to avoid impermissible hindsight reconstruction of an applicant's invention:

> Our case law makes clear that the best defense against the subtle but powerful attraction of hind-sight obviousness analysis is *rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.* Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight.

175 F.3d at 999 (quoting *W.L. Gore & Assoc., Inv. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)) (emphasis added) (citations omitted). *See also In Re Jones*, 958 F.2d 347 ("Conspicuously missing from this record is any evidence, **other than the PTO's speculation (if that can be called evidence)** that one of ordinary skill in the herbicidal art would have been met motivated to make the modification of the prior art salts necessary to arrive at [the claimed invention].").

to look *inside of tissue*. In contrast, *Lackowicz* involves imaging the *surface of tissue*, and therefore does not utilize multiply scattering light. The concept of the use of multiply scattering light is described in detail in the present specification, and a physical analogy was described above in the context of the lifetime of the fluorescent agent. Upon review of these passages, it should be clear that *Lackowicz* does not utilize multiply scattering light. *Lackowicz* does not involve three-dimensional imaging within a tissue, but rather surface images. The above-described teachings on lifetime are not pertinent for surface imaging. In *Lackowicz's* imaging methodology, there is no multiple scattering and photon "time-of-flight" upon which to make comparisons with fluorescent lifetime to. For at least this reason, all claims are allowable in view of *Lackowicz*. Favorable action is requested.
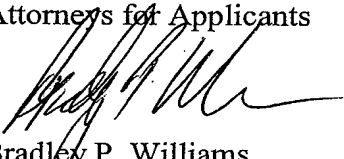
CONCLUSION

Applicants have now made an earnest attempt to place this case in condition for immediate allowance. For the foregoing reasons and for other apparent reasons, Applicants respectfully request allowance of all pending claims.

If the Examiner feels that prosecution of the present Application may be advanced in any way by a telephone conference, the Examiner is invited to contact the undersigned attorney at 214-953-6447.

Applicants do not believe that any fees are due. However, the Commissioner is hereby authorized to charge any fees or credit any overpayments to Deposit Account No. 02-0384 of Baker Botts L.L.P.

Respectfully submitted,

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